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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,819	08/08/2002	John Hughes	A0000005/1-01-MG	5592

7590 10/20/2005

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EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,819	HUGHES ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 27, 2005 has been entered.

Claims 1-17 are pending. Applicant's arguments regarding the pending rejections are addressed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for treating pain associated with diabetic neuropathy using gabapentin or pregabalin with [2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]- carbamic acid benzofuran-2-ylmethyl ester [R-R*,S*)], does not reasonably provide enablement for methods of treating any chronic pain such as causalgia, surgery or traumatic pain, HIV infection, multiple sclerosis, hypothyroidism and anticancer chemotherapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention provides for the combination use of a GABA analog such as gabapentin, or pregabalin with a NK1 receptor antagonist such as [2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]- carbamic acid benzofuran-2-ylmethyl ester [R-R*,S*)].

(2) The state of the prior art

The state of prior art describes the use of exemplified compounds such as gabapentin and [2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-R*,S*)] in treating pain. The prior art is silent as to the entire scope of the genus of NK1 receptor antagonists and GABA analogs for the claimed use. In fact, the state of art does not provide for the entire, so called NK1 receptor antagonists or GABA analogs, nor does the art recognize the instantly exemplified compounds as the penultimate compounds exemplifying the entire genus of compound instantly claimed.

(3) The relative skill of those in the art

The relative skill of those in the art is high and include persons with the knowledge in the art of medical therapeutics, pharmaceutical therapeutics and pharmacology.

(4) The predictability or unpredictability of the art

The unpredictability of the medical and therapeutic art is very high. The true fact of the state of the art is expressed succinctly by Bauer in Pharmacotherapy, A Pathophysiologic Approach, 2nd ed. page 15, 1st para, 1992. Bauer describes that the nature of the applying pharmacological modalities to treat a pathological condition is unpredictable, because there exists at least substantial inter-patient variability. Bauer states "clinicians should never assume that a serum concentration within the therapeutic range will be safe and effective for every patient." Accordingly, the state of art is unpredictable as to the entire scope of the claims and the use of any NK1 receptor antagonist with a GABA analog.

(5) The breadth of the claims

The claims are very broad. It encompasses the use of any compounds described as GABA analog and any NK1 receptor antagonists for treating any pain.

(6) The amount of direction or guidance presented

The specification discloses only gabapentin, or pregabalin with a NK1 receptor antagonist such as [2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-R*,S*)] for treatment of neuropathic pain. The specification provides no guidance, in the way written description, as to treating all typees of pains or conditions associated with HIV infection, multiple sclerosis, hypothyrodism or chemotherapy (as enumerated in the instant claim 9). There is no direct teaching about the minimum period of time required for receptor antagonists to provide the synergistic combination instantly claimed. Neither is there any suggestion as to the type and commonality of effective GABA analogs for the claimed synergy. There is no teaching about the degree of synergy.

Even though the specification may provide for some exemplary drugs from the group of compounds known as GABA analogs or NK1 receptor antagonists, it does not provide necessary link between finding a particular compound or narrowing the range of candidates in order to find a suitable combination without the need for undue experimentation.

Rather, the specification relies on hypothetical level of ordinary skill in the art to supply the missing information. Given the broad breadth of the claims the ordinary skill in the art would not have any guidance as what type of compounds should he proceed with. In fact, the specification appears to rely on the level of ordinary skill in the art to identify suitable candidates and determine degree of synergy for any given condition associated with pain.

It has repeatedly been stressed by the Courts, an assay for determining whether a given compound possesses certain desired characteristics and identifies some broad categories of compound that might work, these descriptions, without more precise guidelines, amount to little more that "a starting point, a direction for further research." See *Genetech v. Novo Nordisk A/S,* 108 F.3d 1361,1366,(Fed. Cir.), also *Enzo Biochem, Inc. V. Calgene*, Inc, 1888 F.3d 1362, 1374 (Fed. Cir. 1999).

In the instant case, for example at page 6-9, specification asserts that the instant methods can employ any compounds described in almost 40 different patent publications. Thus, similar to the cases above, the instant claims appear to place the function of "NK1 antagonism" at the point of novelty by identifying a compound that possesses certain desired characteristic. As has been reasoned, such attempt does not satisfy the statutory requirement set forth under 112 1st para.

The instant claims do not provide any guidance as to compounds employed, nature of therapeutic activity, and further fail to provide notice for those practicing in the art about the limits of protection. Rather, they simply appear to be an invitation to experiment. Thus, practicing the entire scope of the instant claims require undue experimentation.

(7) The presence or absence of working examples

As stated above, the specification merely describes 3 compounds that can be described effective for the instant claims. No other examples describes such outcome with other types of combinations.

(8) The quantity of experimentation necessary

Considering the above-mentioned factors and the fact that there are significant inter-individual variability in using therapeutic compounds, the unpredictability of the nature of art, the extensive risk of adverse events for patients receiving synergistic effects of adverse events, and the burden on one of ordinary skill in the art to perform undue "experimentation study" to determine all the possible effective combination, the entire scope of claims are not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites the limitation "the condition" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. It is not clear whether the synergistic effect are for treating chronic pain or the conditions recited in claim 9.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwell US Patent 5,594,022 in view of Byrans et al, (Medicinal Research Reviews, Vol 19, No. 2, 1999, pages 149-177).

Horwell et al teaches the use of NK1 receptor antagonists for treating pain. (col 2, 8, and 105-106) Horwell also teaches the compound 2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]- carbamic acid benzofuran-2-ylmethyl ester [R-R*,S*)] as an NK1 antagonist (see column 2, line 6, column 8, lines 12-14 and Example 66).

Bryans et al teach the claimed instantly employed GABA analog compounds useful for treating pain. (see pages 163-165).

Both medicaments are taught as useful for treating chronic pain, and neurogenic and neuropathic pain (see claims 42-43).

It is generally considered Prima facie obvious to combine two compounds each of which is taught by the prior ad to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. see In re Kerkhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to combine the NK 1 antagonist described in example 66 of Horwell with gabapentin of Byrans to formulate a combination drug, because they have both been used for the same purpose. Further, it would have been obvious to one of ordinary skill in the art at the time of invention to further optimize the dosages of such individual

compounds and use them to improve the clinical outcome for such pains as neuropathic pain.

5. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Field et al (JPET 1998, 285:1226-1232) ("Field I") in view of Field et al (PAIN 1999, 80:391-398) ("Field II").

Field I describes the use of NK 1 receptor, compound 2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]- carbamic acid benzofuran-2-ylmethyl ester [R-R*,S*)], in animal models for neutopatic pain. (see abstract, page 1229-1231).

Field II describes the use of gabapentin and pregablain in animal models of nueropathic pain. (see abstract, pages 394-397).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to combine the NK 1 recpeor of Field I with the gabapentin or pregablin of Field II to formulate a combination formulation for treatment of neuropathic pain. It would have been further obvious to one of ordinary skill in the art at the time of invention to optimize the dosing and concentration of individual drugs by routine experimentation.

Conclusion

6. **No claims are allowed.** Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The

fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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